Editorial Comments

Are there endogenous molecules that protect kidneys from injury? The case for bone morphogenic protein-7 (BMP-7)

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Keywords: chronic renal fibrosis; epithelial-to-mesenchymal transition (EMT); TGF-beta1; therapy; type 1 collagen

Injury to the kidney can be initiated via diverse mechanisms, such as genetic defects, autoimmune reactions, environmental insults and metabolic defects [1,2]. Based on the kinetics of disease progression, renal injury is traditionally grouped as either being an acute or chronic effect [3,4]. While the kidney displays an enormous potential to regenerate after acute renal injury, chronic renal disease is generally irreversible [1,5,6]. The switch from the normal potential to repair after acute injury, to an irreversible chronic disease phase, is not yet well understood. It has been suggested that an imbalance of growth factors/hormones that regulate renal cell behaviour might play an important role in determining the pathological fate of the kidney [7,8].

Transforming growth factor-beta1 (TGF-β1)

TGF-β1 has been identified as a major effector in the initiation and progression of renal disease [9]. Progression of chronic renal disease correlates with an increase in TGF-β1 expression in the kidney and is also associated with elevated levels of circulating TGF-β1 in the serum [10,11]. TGF-β1 can induce major cellular events associated with renal fibrosis [11]. TGF-β1 can function on podocytes and mesangial cells and thus is a potent mediator of glomerulosclerosis [12–14]. In addition, TGF-β1 is the major activator of fibroblasts and thus enhances interstitial matrix deposition [15]. Furthermore, recent studies have identified TGF-β1 as an inducer of apoptosis and epithelial-to-mesenchymal transition in tubular epithelial cells, potentially contributing to the pathogenesis of tubular atrophy [2,16,17]. In this regard, inhibition of TGF-β1 action has proven to be beneficial for kidney function in various animal models of chronic renal disease [11]. Such laboratory observations have led to recent proposals to test the efficacy of TGF-β1-neutralizing agents in the clinic [11,13].

Bone morphogenic protein-7 (BMP-7)

Interestingly, while TGF-β1 expression increases in acute and chronic renal disease, a protein called BMP-7, another member of the TGF-β superfamily, behaves in the opposite manner [18–20]. In experimental acute renal injury, BMP-7 expression in the kidney is decreased and BMP-7 serum levels are reduced. However, regeneration of the kidney structure is associated with restoration of physiological levels of BMP-7 expression in the kidney [18,19,21]. Therefore, while TGF-β1 is considered as a perpetuator of renal injury, BMP-7 is likely a molecule with a role in protecting the kidney from injury.

BMP-7 was originally identified as a factor that induces bone formation, but studies using BMP-7 knock out mice revealed an important role for BMP-7 in the kidney [22,23]. Genetic deletion of BMP-7 in mice results in microphthalmia, pre-axial polydactyly and—most prominently—in severely dysplastic kidneys, as branching of the epithelium halts after formation of the S-shaped tubules [24,25]. These mice die shortly after birth from renal failure [24,25]. In summary, the important role of BMP-7 in regulating kidney development, its robust expression in the adult kidney, and its reciprocal behaviour in relation to TGF-β1 during renal injury, collectively suggest that BMP-7 might be an important molecule for maintenance of renal homeostasis [26–28]. Such thinking...
provided the necessary rationale for testing recombinant human BMP-7 for its therapeutic potential in the inhibition of renal injury.

Early studies in rats and mice with acute renal injury revealed significant acceleration in the recovery of renal function and histology upon treatment with recombinant human BMP-7 (rhBMP-7) [18]. Similar effects were observed in different chronic models of renal injury in mice and rats [29–35]. In comparative studies, the reno-protective effect of rhBMP-7 was significantly better than the effect of enalapril in rat models of diabetic nephropathy and unilateral urethral obstruction (UUO) [29,36]. More importantly, administration of rhBMP-7 even resulted in regeneration of chronically injured kidneys [35,36].

Recent studies are providing mechanistic insights into how such reno-protective function of BMP-7 might be achieved [35,37]. In tubular epithelial cells, BMP-7 can reverse the epithelial-to-mesenchymal transition by directly counteracting TGF-β1 induced cell signalling [35]. This reversal of the epithelial-to-mesenchymal transition resulted in restoration of tubular homeostasis and improvement of renal function [35]. BMP-7 also decreases the release of pro-inflammatory cytokines from tubular epithelial cells, suggesting that BMP-7 mainly functions as an inducer of tubular cell homeostasis [37,38]. In addition to such effects on tubular epithelial cells, BMP-7 can similarly counteract TGF-β1 mediated pro-fibrotic effects in the mesangial cell [34]. This mechanism potentially accounts for the positive effect of BMP-7 on glomerular function and pathology, which were observed in animal models of diabetic nephropathy [34]. These studies suggest that endogenous BMP-7 functions as a regulator of kidney homeostasis, potentially by countering endogenous TGF-β1 mediated action. During renal injury, when the balance shifts towards TGF-β1 mediated effects (due to an increase of TGF-β1 and/or decrease of BMP-7 signalling), administration of exogenous rhBMP-7 can potentially restore the balance in the kidney to achieve homeostasis. In this regard, an endogenous molecule known as decorin inhibits TGF-β1 activity by trapping it extracellularly and ameliorates progression of TGF-β1 induced chronic renal fibrosis [39].

Conclusion

Such findings with BMP-7 are of considerable interest to nephrologists. If the kidney possesses endogenous molecules, which provide protection from injury, then these molecules could constitute a new line of therapeutic agents against renal failure. Since they are endogenous molecules, toxicity will potentially be minimal or insignificant. The possibility that the kidney itself might be a valuable source for renoprotective molecules, offers new hope for patients suffering from various kidney diseases. The search for these possible new agents with minimal toxicity and side effects must continue at full speed.

The evidence for BMP-7 as an endogenous renoprotective agent is intriguing, yet further studies are needed to evaluate its renoprotective role in humans. Continuing studies will likely provide us with further confidence to test rhBMP-7 in human clinical trials.

Acknowledgements. The authors are supported by grants DK62987 and DK55001 from the NIH, a research fund from the Beth Israel Deaconess Medical Center for the Center for Matrix Biology, a sponsored research grant from Johnson & Johnson and a grant from the Deutsche Forschungsgemeinschaft DFG ZE5231/1 (to M.Z.).

Conflict of interest statement. Research sponsored by Johnson & Johnson.

References

Is there a need for novel cardiovascular risk factors?

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Keywords: coronary heart disease; C-reactive protein; fibrinogen; homocysteine; lipoprotein(a); microalbuminuria; risk factor

Introduction

Atherosclerosis is a multifactorial disease whose age of onset and progression are strongly influenced by inborn and acquired risk factors. Since the pioneering work of the Framingham study, many prospective population and clinical studies have identified a series of independent risk factors for myocardial infarction, stroke and peripheral vascular disease, among which the preexistence of atherosclerotic vascular disease, age, male gender, a positive family history of premature